REMARKS

With this amendment, Claims 29 and 33 have been amended and new Claims 80-99 have been added. After entry of the instant amendment, Claims 29-99 are pending in the instant Application. Applicants gratefully acknowledge the Examiner's statement that the non-statutory obviousness-type double patenting rejection and the anticipation rejections under 35 U.S.C. § 102 rejections have been withdrawn. As will be discussed in more detail below, the claims as pending are believed to be in condition for allowance. For the Examiner's convenience a copy of the claims as pending after entry of the instant amendments is attached hereto as Exhibit B.

I. AMENDMENTS TO THE CLAIMS

With this Amendment Claims 29 and 33 have been amended and new Claims 80-99 have been added. The amendments clarify the claimed compositions. No new matter is added by virtue of these amendments. Claims 29 and 33 have been amended to clarify that the polynucleotides that they recite are for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene. These amendments find support in the Specification at, for example, page 11, line 25 through page 12, line 20. New Claims 80-99 are supported in the Specification at, for example, page 3, line 29 through page 4, line 5, page 13, line 30 through page 14, line 7 and page 24, lines 18-24. Accordingly, entry thereof is respectfully requested.

A. Rejection Of Claims 29-48 Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 29-48 and 69-79 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. Applicants respectfully traverse.

1. The Legal Standard

An Applicant's disclosure satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, if it "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, [the Applicant] was in possession of *the invention*." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (emphasis in original). The invention is whatever is now claimed. *See id.*

The Examiner cites several cases that interpret the written description requirement as it pertains to nucleic acids. In *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) the court considered whether a Specification teaching a method of isolating a fragment of an gene and a method of isolating an mRNA encoding the gene, but not the sequence of the gene or its mRNA, provided adequate written description for an interference count reading "[a] DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." In *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), the court considered whether a Specification disclosing only the sequence of a rat insulin cDNA provided adequate written description for claims directed generally to all vertebrate or mammalian insulin cDNAs.

2. The Rejected Claims Satisfy The Written Description Requirement Of *University of California*

The rejected claims satisfy the written description requirement enunciated by the Federal Circuit in *University of California*. In *University of California* the court found the disputed patent's written description inadequate because "[o]ne skilled in the art cannot, as one can do with a fully described genus, visualize *or recognize* the identity of the members of the genus." *University of California*, 43 USPQ2d at 1406 (emphasis added). Applicants' Specification easily satisfies this standard. Applicants' claimed polynucleotides are distinguished from other polynucleotides by *specifically defined structural features* (*i.e.*, the sequences disclosed in Figures 1 and 2, the polymorphisms of Table 1 and the length ranges appearing in the Specification *passim*). Accordingly, Applicants provide structural information for *every claimed polynucleotide*. Consequently, one of skill in the art can *recognize* all of the members of each of Applicants' claimed genera. Thus, Applicants have satisfied the written description requirement as it is formulated in *University of California*. Applicants therefore respectfully request that the instant rejection be withdrawn.

3. There Is No Legal Basis For Rejecting Claims Because They Use The Transition Phrase "Comprising"

Applicants gratefully acknowledge the Examiner's statement that claims *consisting of* the genera of sequences recited by the rejected claims would satisfy the written description requirement. However, the Examiner asserts that claims *comprising* these sequences do not

satisfy the written description requirement. Thus, the instant rejection is premised entirely on Applicants' choice of transition phrase. Applicants respectfully traverse.

Applicants respectfully point out that a rejection based on the use of the transition phrase "comprising" is not supported by a recognized rule of law. The Patent Office routinely issues patents with claims reciting nucleic acids "comprising" a fragment of a disclosed nucleotide sequence. *See, e.g.*, U.S. Pat. No. 6,300,485, Claim 1 ("An isolated nucleic acid molecule *comprising* a polynucleotide selected from the group consisting of: ... c) a polynucleotide *comprising* at least about 390 contiguous bases from the coding region of SEQ ID NO:2...") (emphases added); U.S. Pat. No. 6,303,772, Claim 10 ("An isolated nucleic acid *comprising* nucleotides -225 to +56 of FIG. 13, nucleotides 76-356 of SEQ ID NO:34.") (emphasis added); U.S. Pat. No. 6,300,094, Claim 1 ("An isolated polynucleotide segment, *comprising* a first polynucleotide sequence or the full complement of the entire length of the first polynucleotide sequence, wherein the first polynucleotide sequence *comprises* nucleotides 2655 to 3353 of SEQ ID NO:1.") (emphases added).[1] Applicants are unaware of a difference between the claims in the these patents and the rejected claims of the instant Application that would support a rejection of the latter but not the former.

More to the point, all of the pending claims of the instant Application, whether they use the transition phrase "comprising," "consisting of" or "consisting essentially of" satisfy the standard of written description from *University of California* quoted above. The Examiner apparently agrees that one of ordinary skill in the art, guided by Applicants' disclosure, can *with complete accuracy* recognize whether *any* particular polynucleotide falls within or without the literal scope of any one of Claims 49-68, which use the transition phrase "consisting of," simply by determining whether the nucleic acid is of the recited length, whether the nucleic acid's sequence matches a subsequence of SEQ ID NO:1 or SEQ ID NO:2, and whether that subsequence contains one or more of the polymorphisms recited in the claim. Applicants respectfully point out that the rejected claims satisfy the same standard of written description. One of ordinary skill, guided by Applicants' disclosure, can *with complete accuracy* recognize whether *any* particular nucleic acid falls within or without the literal scope of any one of Claims 37-48 or 69-79, which use the transitional phrase

[1] All of these patents issued in October 2001, years after each of the cases cited against Applicants were decided.

"comprising," simply by determining whether the nucleic acid *contains anywhere within it* a subsequence of the recited length that matches a subsequence of SEQ ID NO:1 or SEQ ID NO:2 and whether the matching subsequences contain one or more of the polymorphisms recited in the claim. One of ordinary skill in the art also can recognize with complete accuracy whether any polynucleotide falls within the literal scope of any one of Claims 29-36 by following the same steps, and by additionally determining whether the polynucleotide is useful for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene,[2] as explained in the Specification at, for example, page 14, line 10 through page 16, line 15. As the Examiner states in the instant Office Action, *University of California* does not forbid the use of a functional limitation to distinguish claimed subject matter from non-claimed subject matter. *University of California* states only that a claimed cDNA cannot be defined *solely* by a functional limitation (*e.g.*, only by the name of the protein encoded by the cDNA, in the absence of any structural or other information about the cDNA itself).

Thus, the rejected claims satisfy the standards for written description established by the courts and followed by the Patent Office. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

4. The Facts Of The Instant Case Are Distinguishable From The Facts Of *University of California*

The courts have repeatedly emphasized that written description is a fact-specific issue. *See id.* at 1116 ("the precedential value of cases in this area [*i.e.*, written description] is extremely limited" quoting *In re Driscoll*, 195 USPQ 434, 438 (C.C.P.A. 1977)). Thus, it is necessary to consider the specific facts of the cases cited by the Examiner as supporting a finding of lack of written description and compare them with the facts of the instant case.

The Examiner asserts that the facts of the instant case are not distinguishable from the facts of *University of California* for several reasons. First, the Examiner emphasizes that the applicants in *University of California* attempted to define their claimed nucleic acids solely

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[2] While, as explained herein, every *polymorphism* in Table 1 is unquestionably useful for determining whether a subject has an increased likelihood of carrying the 24D1 allele, it is possible that some of the *polynucleotides* comprising them are not useful for this purpose. For example, one of ordinary skill in the art would appreciate that a polynucleotide consisting of $(CA)_{25}$ is not useful for distinguishing the disease-associated $(CA)_{17}$ allele from the wild-type associated allele $(CA)_{16}$ at nucleotides 1-36 of the 235 kb sequences disclosed in the instant Specification.

by function. Applicants agree with this statement, as stated in their previous response. However, unlike *University of California*, Applicants in the instant case define *each* claimed sequence in *each* pending claim by function *and* by structure (for Claims 29-36) or by structure alone (for Claims 37-79). Thus, the rejected claims of the instant application are distinguished from the claims at issue in *University of California*. Second, the Examiner asserts that:

> It is readily apparent to anyone of ordinary skill in the art the gene of interest is not large enough to occupy the entire disclosed sequence, therefore the instant specification comes no closer to identifying a given gene..... [U]nless the HH-associated gene occupies the entire sequence and all the polymorphic sites are involved in the pathology, the structure of the gene Applicant intends to identify is no better defined because the instant specification does not disclose where in the 470 kilobases of disclosed sequence information the gene of interest is located, nor does it disclose which polymorphic sites are of predictive value.

Office Action at page 4. This statement fails to provide a basis for rejecting Claims 29-48 and 69-79 for at least three reasons. First, Applicants respectfully point out that the Examiner apparently has misapprehended the claimed invention. *Applicants do not claim, as such, an "HH-associated gene."* The present Application describes and claims polynucleotides useful for determining whether a subject has an increased likelihood of having the disease-causing 24D1 allele of the HH gene. As explained herein, Applicants provide structural information for *every* claimed polynucleotide. This is a critical difference between the claims at issue in *University of California* and the rejected claims of the instant application.

Second, Applicants explicitly disclose in the Specification the polymorphic sites that are of predictive value. The Examiner's assertion to the contrary is simply incorrect. As stated in the Specification, *all of the 397 unique polymorphic sites listed in Table 1 are of predictive value. See* the Specification at, for example, page 12, line 34 through page 13, line 6. Two independent lines of evidence indicate that this statement is correct. The first line of evidence is empirical: markers as far apart as 2,000 kb (2 Mb) on Chromosome 6 are linked to the HH gene. *See* Raha-Chowdhury *et al.*, 1995, Hum. Mol. Genet. 4:1869-74 ("The haemochromatosis gene . . . is linked to both HLA-A and D6S105 on the short arm of chromosome 6 *but these markers are separated by approximately 2 Mb of DNA.*") (emphasis added). All of the 397 unique polymorphisms disclosed in the instant Specification and

recited in the pending claims are within about 200 kb (0.2 Mb) of the HH gene, as explained below, and so must be tightly linked to it. The second line of evidence derives from a simple calculation. Multiplying the average map distance per physical length unit of Chromosome 6 (1.12 cM per 1 Mb (sex average), *see* Venter *et al.*, 2001, Science 291:1304-51 at Table 12) by the physical length of the region comprising the HH gene and all of the polymorphisms in Table 1 (0.235 Mb, see above) produces a map distance of 0.26 cM. One of skill in the art will understand that any two genetic markers located within 0.26 cM of one another are, by definition, very tightly linked to each other. Thus, each one of the 397 unique polymorphisms identified in the instant Specification is tightly linked to the HH gene. The Specification further teaches that the presence in an individual of *any* combination of *any* two or three of the disease-associated alleles of the polymorphisms listed in Table 1 indicates that that individual is more likely to carry at least one copy of the disease-causing 24D1 allele of the HH gene, and, at page 12, lines 21-33, that the disease-associated alleles of the polymorphisms at, for example, positions 35,983 and 61,465 are so rare in the general population that the detection of one of these alleles in a subject is sufficient to determine that the subject has an increased risk of carrying the 24D1 allele. Thus, the present Specification explicitly teaches that *all* of the polymorphisms in Table 1 are associated with HH.

Third, the instant Specification discloses the precise sequence and location of the HH gene. The Examiner's assertion to the contrary is incorrect. Applicants and their colleagues disclosed the sequence and precise chromosomal location of the HH gene in U.S. Pat. No. 6,025,130 ("the '130 patent"), which issued from U.S. Pat. App. No. 08/652,265 and is *incorporated in the instant Application by reference in its entirety*. *See* the Specification at page 1, lines 22 and 23. As disclosed in the '130 patent, the HH gene is approximately 11kb long, including introns, and the 24D1 mutation occurs almost exactly in the middle of this sequence. *See* the '130 patent at Figure 3 and column 9, lines 15-30. The 24D1 mutation is located at nucleotide 41,316 of the 235kb sequence disclosed in the present application. *See* Specification at page 27, line 16. Thus, the HH gene occupies the region spanning residues 35,842 and 46,307 of the 235 kb sequence disclosed in the instant Specification.

Thus, the reasons cited by the Examiner for equating the facts of the instant case to the facts relied on by the Federal Circuit in *University of California* are not supported by the

evidence of record. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

5. **The Facts Of The Instant Case Are Distinguishable From The Facts Of *Fiers***

The Examiner also asserts that the written description requirement as enunciated in *Fiers* supports the rejection of Claims 29-48 and 69-79 because the instant Specification allegedly does not disclose which polymorphisms are associated with HH and which are associated with the pathology. As explained above, this is simply incorrect. The Examiner further asserts that the instant Specification is not distinguishable from *Fiers* because "it is readily apparent to anyone of ordinary skill in the art the gene of interest is not large enough to occupy the entire disclosed sequence, therefore the instant specification comes no closer to identifying a given gene." As explained above, the rejected claims do not recite an "HH-encoding nucleic acid" as such, and the location and sequence of the HH gene are incorporated into the instant Specification by reference to the '130 patent. Thus, the reasons cited by the Examiner for equating the facts of the instant case to the facts relied on by the Federal Circuit in *Fiers* are not supported by the evidence of record. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

B. **Rejection Of Claims 29-79 Under 35 U.S.C. §101**

Claims 29-79 are rejected under 35 U.S.C. § 101 for allegedly lacking utility. As Applicants have asserted a credible, specific and substantial utility for the claimed invention, Applicants respectfully traverse.

1. **The Legal Standard**

According to 35 U.S.C. § 101, whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter may obtain a patent therefor subject to the conditions and requirements of 35 U.S.C. The threshold of utility is not high. *See Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700, 1702 (Fed. Cir. 1999). An invention is "useful" under 35 U.S.C. § 101 if it is capable of providing some identifiable benefit. *Id.* (*citing Brenner v. Manson*, 383 U.S. 519, 534, 148 USPQ 689, 695 (1966)).

2. **Hereditary Hemochromatosis**

HH is an inherited disorder of iron metabolism wherein the body accumulates excess iron. In symptomatic individuals, this excess iron leads to deleterious effects by being deposited in a variety of organs leading to their failure, and resulting in cirrhosis, diabetes, sterility, and other serious illnesses. *See* the Specification at page 1, lines 16-21. HH is typically inherited as a recessive trait; in the current state of knowledge, homozygotes carrying two defective copies of the gene are most frequently affected by the disease. In addition, heterozygotes for the HH gene are more susceptible to sporadic porphyria cutanea tarda and potentially other disorders. It is estimated that approximately 10-15% of individuals of Northern European descent carry one copy of the HH gene mutation and that there are about one million homozygotes in the United States. HH, thus, represents one of the most common genetic disease mutations in individuals of Northern European descent. Although ultimately HH produces debilitating symptoms, the majority of homozygotes and heterozygotes have not been diagnosed. *See id.* at page 1, line 24 through page 2, line 3. Although blood iron parameters can be used as a screening tool, a confirmed diagnosis often employs liver biopsy which is undesirably invasive, costly, and carries a risk of mortality. *See id.* at page 3, lines 23-26.

3. **The Utility Of The Claimed Invention**

It appears that about 80% to 90% of all HH patients carry at least one copy of the disease-causing 24D1 allele of the HH gene. The 24D1 allele, which also is called the common ancestral mutation, is closely linked to specific alleles of certain genetic markers. *See id.* at page 2, lines 21-25. In the instant Specification, Applicants disclose the location and sequence of 397 previously unknown polymorphisms that are tightly genetically linked to the disease-causing 24D1 allele of the HH gene. Thus, each one of these polymorphisms is a genetic marker for the disease-causing 24D1 allele of the HH gene. Consequently, the claimed polynucleotides, each of which encompasses at least one of these polymorphisms, can be used to determine whether a subject has an increased likelihood of being heterozygous or homozygous for the disease-causing 24D1 allele of the HH gene.

4. **Applicants Have Asserted A Credible, Specific and Substantial Utility F r The Rejected Claims**

Applicants gratefully acknowledge the Examiner's statement that the association of a particular polymorphism with a pathology would be both specific and substantial. However, the Examiner concludes that this association has not been established for any of the polymorphisms in Table 1. The Examiner bases this conclusion on two incorrect assertions. First, that the location of the HH gene within the 235 kb chromosomal sequences of SEQ ID NOS: 1 and 2 is not disclosed; second, that no polymorphisms are identified that are close enough to the HH gene to be useful for diagnostic purposes. As explained above, the precise location of the HH gene in this region and its sequence are disclosed in U.S. Pat. No. 6,025,130, which issued from U.S. Pat. App. No. 08/652,265 and is incorporated in its entirety by the present Specification. *See* the Specification at page 1, lines 7-13. Consequently, Applicants do not seek a "hunting license" to find and characterize the HH gene. Applicants also disclose that *all* of the polymorphisms disclosed in Table 1 are associated with the disease-causing 24D1 allele of the HH gene and provide two independent lines of objective evidence supporting this statement, as explained above. Thus, as all of the claimed polynucleotides comprise at least one of these polymorphisms, one of ordinary skill in the art appreciates that all of the claimed polynucleotides are useful for determining whether a subject has an increased likelihood of having the disease-associated 24D1 allele of the HH gene. This is an association between the polymorphisms and a pathology and so satisfies the Examiner's standard for a specific and substantial utility. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

C. **Rejection Of Claims 29-79 Under 35 U.S.C. §112, First Paragraph (Enablement)**

Claims 29-79 are rejected for allegedly lacking enablement under 35 U.S.C. § 112, first paragraph. The sole basis for this rejection is the alleged lack of utility of the rejected claims. As Applicants have explained above, each of the rejected claims has a specific and credible utility. Thus, Applicants respectfully request that the instant rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be considered and made of record in the file history of the instant application. Applicants

submit that Claims 29-99 meet all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore respectfully requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date October 24, 2001

47,763
Nathan A. Machin (Reg. No.)

for Brian M. Poissant (Reg. No. 28,462)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, N.Y. 10036-2711
(212) 790-9090

Exhibit A
Serial N .: 08/852,495
Marked-Up Copies of Amended Claims

29. (Three Times Amended) An isolated polynucleotide for [diagnosing hereditary hemochromatosis] determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene comprising at least 8 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

33. (Three Times Amended) An isolated polynucleotide for [diagnosing hereditary hemochromatosis] determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene comprising at least 18 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

Exhibit B
Serial No.: 08/852,495
Claims As Pending After Entry Of The Instant Amendments

29. (Three Times Amended) An isolated polynucleotide for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene comprising at least 8 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

30. (Amended) The isolated polynucleotide of Claim 29, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

31. (Amended) The isolated polynucleotide of Claim 29, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

32. (Amended) A pair of isolated polynucleotides as in Claim 29.

33. (Three Times Amended) An isolated polynucleotide for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene comprising at least 18 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

34. (Amended) The isolated polynucleotide of Claim 33, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

35. (Amended) The isolated polynucleotide of Claim 33, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

36. (Amended) A pair of isolated polynucleotides as in Claim 33.

37. (Amended) An isolated polynucleotide comprising a fragment of at least about 100 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

38. (Amended) The isolated polynucleotide of Claim 37 which is cDNA.

39. (Amended) The isolated polynucleotide of Claim 37 which is RNA.

40. (Amended) The isolated polynucleotide of Claim 37 which is genomic DNA.

41. (Amended) An isolated polynucleotide comprising a fragment of at least about 300 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

42. (Amended) The isolated polynucleotide of Claim 41 which is cDNA.

43. (Amended) The isolated polynucleotide of Claim 41 which is RNA.

44. (Amended) The isolated polynucleotide of Claim 41 which is genomic DNA.

45. (Amended) A kit comprising an isolated polynucleotide of Claim 29.

46. (Amended) A kit comprising an isolated polynucleotide of Claim 33.

47. (Amended) A kit comprising at least one pair of isolated polynucleotides as in Claim 32.

48. (Amended) A kit comprising at least one pair of isolated polynucleotides as in Claim 36.

49. An isolated polynucleotide consisting of at least 8 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

50. The isolated polynucleotide of Claim 49, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

51. The isolated polynucleotide of Claim 49, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

52. A pair of isolated polynucleotides as in Claim 49.

53. A kit comprising an isolated polynucleotide of Claim 49.

54. A kit comprising at least one pair of isolated polynucleotides as in Claim 52.

55. An isolated polynucleotide consisting of at least 18 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

56. The isolated polynucleotide of Claim 55, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

57. The isolated polynucleotide of Claim 55, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

58. A pair of isolated polynucleotides as in Claim 55.

59. A kit comprising an isolated polynucleotide of Claim 55.

60. A kit comprising at least one pair of isolated polynucleotides as in Claim 58.

61. An isolated polynucleotide consisting of a fragment of at least about 100 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

62. The isolated polynucleotide of Claim 61 which is cDNA.

63. The isolated polynucleotide of Claim 61 which is RNA.

64. The isolated polynucleotide of Claim 61 which is genomic DNA.

65. An isolated polynucleotide consisting of a fragment of at least about 300 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

66. The isolated polynucleotide of Claim 65 which is cDNA.

67. The isolated polynucleotide of Claim 65 which is RNA.

68. The isolated polynucleotide of Claim 65 which is genomic DNA.

69. An isolated polynucleotide comprising at least 8 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS: 1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site selected from the group consisting of polymorphic sites listed in the following table:

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
841	T-C
2662-2663	TT DEL
3767	T-C
3829	C-G
4925-4928	TAAA DEL
5691	C-T
5839	T-C
6011	G-A
6047	C-G
6231	G-A
6643	ADEL

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
6698	T-C
7186	T-C
7273	G-A
7545-7558	TCACACACCGATTGG DEL (SEQ ID NO:17)
7672	G DEL
7933	T-C
8746	T-G
9115	G-A
9823	G-A
10027	G-A
10214	C-T
10828	A-G
10918	C-G
10955	A-G
11524	C-A
11674	A-G
11955	T-C
12173-12175	TTT DEL
13304	G-A
13455	G-A
14416-14417	A INS
14998	C-T
15564	T-C
15887	A-G
15904-1 5919	CCAAACTGATCTTTGA DEL (SEQ ID NO:18)
16019	T DEL
16211	A-T
17461	A-G
19755	G-A
19949	C-T
20085	C-T
20366-20367	A INS
20463	C-A
20841	A-T
21059	A-T
21117	A-G
21837	A-C
22293	A-C
22786	C-A
23009	G-A
24143	T-A
26175	G-C
26667	C-A
26994	T-C
27838	G-T
27861	T DEL
28132	G-A
29100	G-A
29454-29457	TTTT DEL
29787	T-G
29825	A-C
30009	T-C

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
30177	A-G
30400	A-G
31059	T-A
31280	C-T
31749	C-T
32040	C-G
33017	T-G
33026	T DEL
34434	C-T
35179	A-C
35695	G-A
35702	G-A
35983	A-G
37411	A-G
38526	C-T
40431	C-A
42054-42055	TT DEL
43783-43784	TTTT INS
45120	C DEL
45567	A-C
46601	A-T
47255	C-G
47758	C-A
47994	G-C
48440	G-A
48650	T-G
48680	A-G
50240	C-T
50553	G-A
50586	G-T
51322	G-C
51747	A-G
52474	C-G
52733	C-A
52875	G-A
53707	G-A
54819	A-G
55913	T-C
56225	A-C
56510	T-C
56566	G-A
56618	A-T
57815	A-G
58011	T DEL
58247-58248	T INS
58926	C-G
59406	C-G
59422	G-C
60221-60222	A INS
60656-60657	CA DEL
61162	G-A
61465	G-A
61607	A DEL
61653	T-C

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
61794-61795	T INS
62061	G-C
62362	T-G
62732	C-G
63364	G-A
63430-63431	GT INS
63754	C-T
63785	A-C
63870-63871	A INS
64788	A-G
64962	G-A
65891	C-T
66675	G-C
67186-67187	ATT INS
67746-67747	TT INS
68259	T-C
68836	T-C
68976	C-G
72508	T-G
72688	C-G
75323-75324	T INS
75887	G-C
77519	T-C
77749	G-A
77908	T-C
78385	C-G
78592-78593	AG INS
80189	T-G
80279	T DEL
80989-80990	A INS
81193	T-C
81273	A DEL
82166	G-A
83847	T DEL
84161-84162	CA-GG
84533	A-G
84638	T-G
85526	T-G
85705	G-T
86984	T-C
87655	T-C
87713	A-C
87892	C-T
88192	T DEL
88528	A-G
89645	A-T
89728	A-G
90088	T-C
91193-91194	2209bp INS
91373	T-C
91433-91434	A INS
91747	G-A
93625	T DEL
95116-95117	T INS

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
96315	G-A
97981	A-G
98351	T DEL
99249	C-T
100094-1 00095	T INS
100647-100648	TTC INS
100951	C-T
101610	C-G
102589	C-T
103076-1 03077	TATATATATATATA INS (SEQ ID NO:19)
103747	T-C
105638	A-C
107024	C-T
107322	C-T
107858	C-G
109019	A DEL
109579	T DEL
110021	C-A
111251	C-A
111425	G-A
112644	T-A
113001	G-C
113130	C-T
114026	G-A
114250	A DEL
115217	C-G
117995	G-A
118874	A-G
119470	T-C
119646	G-T
120853	C-T
121582	G-A
123576	A-C
125581	C-T
125970	G-T
126197	A-G
126672	A DEL
126672	G-C
128220-128221	A INS
132569	C-T
133572	A-C
134064	T-G
136999	G-A
137784	C-T
138903	G-A
1391 59-1 39160	A INS
140359	G-A
140898	C-T
141313	C DEL
141343	T-C
142148	T-C
142178	C-A
142433-1 42434	ATAGA INS

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
143783	C-T
144090	C-T
144220-144221	A INS
144725	A-C
145732-145733	AAAAAAAAAAAAAA INS (SEQ ID NO:20)
147016-147017	CG DEL
147021	G-T
147536	T-G
148936	T-A
149061	T-C
154341	A-T
154588	G-A
155464	G-A
158574	C-G
160007	C-T
164348	A-T
164499	C-G
166677-166678	AAAG INS
167389	G-A
168506-168507	AGGATGGTCT INS (SEQ ID NO:21)
168515	T-C
169413-169414	AA INS
170300-170301	TTGTTGTTGTTG INS (SEQ ID NO:22)
170491	G-A
173428	T-C
173642	G-A
173948	T-G
175330	T-C
175836	T-C
176200	G-C
176222	T-C
176524	A-T
176684	G-A
176815	T-C
177049	T-C
177065	G-T
178285	T-C
179114-179115	A INS
179260	C-G
179281	C-G
180023	G-C
180430	T-C
180773	T-C
180824	T-C
181097	C-T
181183	A-T
182351	C-T
183197	G-A
183623	A-T
183653	G-T
183657	T-G

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
183795-183796	A INS
184060	G-A
184993	G-A
185918	A-G
186036	T-C
186506-186507	TAAC INS
186561-186568	TATTTATT DEL
186690	G DEL
186751	T-A
187221	A-G
187260	A-G
187444-187447	CTCT DEL
187831-187832	C INS
188638	G-A
188642	C-T
189246	T-C
190340	A-C
190354	A-G
190762	A-G
191260	G-T
193018-193019	AGAT INS
193147	T-G
193196-193197	C INS
193499	C-T
193738	C-G
193984-193985	ACACACAC INS
194064	C-G
194504	A DEL
194734	G-A
194890	A-C
195404	G-A
195693	A-T
196205	G-A
197424	C-T
197513	C-T
197670	G-A
198055	C-A
198401	C-T
198692	A-G
198780	T DEL
199030	T-G
199933	C-T
200027	G-A
200439	T-A
200452	A-G
200472-200483	AATAATAATAAT DEL (SEQ ID NO:24)
200559	A-T
200745	A-G
200919	T-A
201816	C-T
201861-201862	42bp INS
202662	T-C
202880	T-C

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
204341	C-T
204768	A-T
205284	T-G
207400	C-A
208634	T-C
208718	T DEL
208862	A-C
209419-209420	TT DEL
209802	G-A
209944	C-G
210299	A-G
211142	G-A
212072	G-A
212146	T-C
212379	G-A
212637-212639	TCTDEL
212696	T-C
213042	T-A
214192	A-G
214549	T-C
214795	C-T
214908	T-G
214977	A-G
215769	C-T
215947	C-A
216232	A-G
217478	G-A
219052	T-C
219082-219083	ATATATATATATATATATAT INS
219314	C-A
219327	G-A
219560	C-T
219660	C-T
219889	G-A
220198	G-T
220384	G-A
220451-220452	CAAAAA INS
221363	G-A
221645	G-A
222119	T-C
222358	A-G
222367	A-C
222686	A-G
222959	T-C
223270-223271	TT DEL
223283	T-C
224964	T-C
225232	A-C
225416	G-C
225486	T-C
226088	A-G
228421	A-G
230047	G-A

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
230109	G-C
230376	C-G
230394	A-C
231226	A-G
231447	G-A
231835	A-G
232400-232402	AAA DEL
232402-232403	G INS
232515	G-C
232703	G-T
232750	A-G

70. The isolated polynucleotide of Claim 69, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

71. The isolated polynucleotide of Claim 69, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

72. A pair of isolated polynucleotides as in Claim 69.

73. A kit comprising an isolated polynucleotide of Claim 69.

74. A kit comprising at least one pair of isolated polynucleotides as in Claim 72.

75. An isolated polynucleotide comprising at least 18 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS: 1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site selected from the group consisting of polymorphic sites listed in the following table:

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
841	T-C
2662-2663	TT DEL
3767	T-C
3829	C-G
4925-4928	TAAA DEL
5691	C-T
5839	T-C
6011	G-A
6047	C-G
6231	G-A
6643	A DEL
6698	T-C
7186	T-C
7273	G-A
7545-7558	TCACACACCGATTGG DEL (SEQ ID NO:17)
7672	G DEL
7933	T-C
8746	T-G
9115	G-A
9823	G-A

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
10027	G-A
10214	C-T
10828	A-G
10918	C-G
10955	A-G
11524	C-A
11674	A-G
11955	T-C
12173-12175	TTT DEL
13304	G-A
13455	G-A
14416-14417	A INS
14998	C-T
15564	T-C
15887	A-G
15904-1 5919	CCAAACTGATCTTTGA DEL (SEQ ID NO:18)
16019	T DEL
16211	A-T
17461	A-G
19755	G-A
19949	C-T
20085	C-T
20366-20367	A INS
20463	C-A
20841	A-T
21059	A-T
21117	A-G
21837	A-C
22293	A-C
22786	C-A
23009	G-A
24143	T-A
26175	G-C
26667	C-A
26994	T-C
27838	G-T
27861	T DEL
28132	G-A
29100	G-A
29454-29457	TTTT DEL
29787	T-G
29825	A-C
30009	T-C
30177	A-G
30400	A-G
31059	T-A
31280	C-T
31749	C-T
32040	C-G
33017	T-G
33026	T DEL
34434	C-T
35179	A-C

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
35695	G-A
35702	G-A
35983	A-G
37411	A-G
38526	C-T
40431	C-A
42054-42055	TT DEL
43783-43784	TTTT INS
45120	C DEL
45567	A-C
46601	A-T
47255	C-G
47758	C-A
47994	G-C
48440	G-A
48650	T-G
48680	A-G
50240	C-T
50553	G-A
50586	G-T
51322	G-C
51747	A-G
52474	C-G
52733	C-A
52875	G-A
53707	G-A
54819	A-G
55913	T-C
56225	A-C
56510	T-C
56566	G-A
56618	A-T
57815	A-G
58011	T DEL
58247-58248	T INS
58926	C-G
59406	C-G
59422	G-C
60221-60222	A INS
60656-60657	CA DEL
61162	G-A
61465	G-A
61607	A DEL
61653	T-C
61794-61795	T INS
62061	G-C
62362	T-G
62732	C-G
63364	G-A
63430-63431	GT INS
63754	C-T
63785	A-C
63870-63871	A INS
64788	A-G

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
64962	G-A
65891	C-T
66675	G-C
67186-67187	ATT INS
67746-67747	TT INS
68259	T-C
68836	T-C
68976	C-G
72508	T-G
72688	C-G
75323-75324	T INS
75887	G-C
77519	T-C
77749	G-A
77908	T-C
78385	C-G
78592-78593	AG INS
80189	T-G
80279	T DEL
80989-80990	A INS
81193	T-C
81273	A DEL
82166	G-A
83847	T DEL
84161-84162	CA-GG
84533	A-G
84638	T-G
85526	T-G
85705	G-T
86984	T-C
87655	T-C
87713	A-C
87892	C-T
88192	T DEL
88528	A-G
89645	A-T
89728	A-G
90088	T-C
91193-91194	2209bp INS
91373	T-C
91433-91434	A INS
91747	G-A
93625	T DEL
95116-95117	T INS
96315	G-A
97981	A-G
98351	T DEL
99249	C-T
100094-1 00095	T INS
100647-100648	TTC INS
100951	C-T
101610	C-G
102589	C-T

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
103076-1 03077	TATATATATATATA INS (SEQ ID NO:19)
103747	T-C
105638	A-C
107024	C-T
107322	C-T
107858	C-G
109019	A DEL
109579	T DEL
110021	C-A
111251	C-A
111425	G-A
112644	T-A
113001	G-C
113130	C-T
114026	G-A
114250	A DEL
115217	C-G
117995	G-A
118874	A-G
119470	T-C
119646	G-T
120853	C-T
121582	G-A
123576	A-C
125581	C-T
125970	G-T
126197	A-G
126672	A DEL
126672	G-C
128220-128221	A INS
132569	C-T
133572	A-C
134064	T-G
136999	G-A
137784	C-T
138903	G-A
1391 59-1 39160	A INS
140359	G-A
140898	C-T
141313	C DEL
141343	T-C
142148	T-C
142178	C-A
142433-1 42434	ATAGA INS
143783	C-T
144090	C-T
144220-144221	A INS
144725	A-C
145732-145733	AAAAAAAAAAAAAA INS (SEQ ID NO:20)
147016-147017	CG DEL
147021	G-T
147536	T-G

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
148936	T-A
149061	T-C
154341	A-T
154588	G-A
155464	G-A
158574	C-G
160007	C-T
164348	A-T
164499	C-G
166677-166678	AAAG INS
167389	G-A
168506-168507	AGGATGGTCT INS (SEQ ID NO:21)
168515	T-C
169413-169414	AA INS
170300-170301	TTGTTGTTGTTG INS (SEQ ID NO:22)
170491	G-A
173428	T-C
173642	G-A
173948	T-G
175330	T-C
175836	T-C
176200	G-C
176222	T-C
176524	A-T
176684	G-A
176815	T-C
177049	T-C
177065	G-T
178285	T-C
179114-179115	A INS
179260	C-G
179281	C-G
180023	G-C
180430	T-C
180773	T-C
180824	T-C
181097	C-T
181183	A-T
182351	C-T
183197	G-A
183623	A-T
183653	G-T
183657	T-G
183795-183796	A INS
184060	G-A
184993	G-A
185918	A-G
186036	T-C
186506-186507	TAAC INS
186561-186568	TATTTATT DEL
186690	G DEL
186751	T-A

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
187221	A-G
187260	A-G
187444-187447	CTCT DEL
187831-187832	C INS
188638	G-A
188642	C-T
189246	T-C
190340	A-C
190354	A-G
190762	A-G
191260	G-T
193018-193019	AGAT INS
193147	T-G
193196-193197	C INS
193499	C-T
193738	C-G
193984-193985	ACACACAC INS
194064	C-G
194504	A DEL
194734	G-A
194890	A-C
195404	G-A
195693	A-T
196205	G-A
197424	C-T
197513	C-T
197670	G-A
198055	C-A
198401	C-T
198692	A-G
198780	T DEL
199030	T-G
199933	C-T
200027	G-A
200439	T-A
200452	A-G
200472-200483	AATAATAATAAT DEL (SEQ ID NO:24)
200559	A-T
200745	A-G
200919	T-A
201816	C-T
201861-201862	42bp INS
202662	T-C
202880	T-C
204341	C-T
204768	A-T
205284	T-G
207400	C-A
208634	T-C
208718	T DEL
208862	A-C
209419-209420	TT DEL
209802	G-A

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
209944	C-G
210299	A-G
211142	G-A
212072	G-A
212146	T-C
212379	G-A
212637-212639	TCTDEL
212696	T-C
213042	T-A
214192	A-G
214549	T-C
214795	C-T
214908	T-G
214977	A-G
215769	C-T
215947	C-A
216232	A-G
217478	G-A
219052	T-C
219082-219083	ATATATATATATATATATAT INS
219314	C-A
219327	G-A
219560	C-T
219660	C-T
219889	G-A
220198	G-T
220384	G-A
220451-220452	CAAAAA INS
221363	G-A
221645	G-A
222119	T-C
222358	A-G
222367	A-C
222686	A-G
222959	T-C
223270-223271	TT DEL
223283	T-C
224964	T-C
225232	A-C
225416	G-C
225486	T-C
226088	A-G
228421	A-G
230047	G-A
230109	G-C
230376	C-G
230394	A-C
231226	A-G
231447	G-A
231835	A-G
232400-232402	AAA DEL
232402-232403	G INS

POLYMORPHIC SITE IN SEQ ID NO:1	POLYMORPHISM
232515	G-C
232703	G-T
232750	A-G

76. The isolated polynucleotide of Claim 75, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

77. The isolated polynucleotide of Claim 75, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

78. A pair of isolated polynucleotides as in Claim 75.

79. A kit comprising an isolated polynucleotide of Claim 75.

80. (New) An isolated polynucleotide for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene consisting essentially of at least 8 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

81. (New) The isolated polynucleotide of Claim 80, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

82. (New) The isolated polynucleotide of Claim 80, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

83. (New) A pair of isolated polynucleotides as in Claim 80.

84. (New) A kit comprising an isolated polynucleotide of Claim 80.

85. (New) An isolated polynucleotide for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene consisting essentially of at least 18 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

86. (New) The isolated polynucleotide of Claim 85, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

87. (New) The isolated polynucleotide of Claim 85, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

88. (New) A pair of isolated polynucleotides as in Claim 85.

89. (New) A kit comprising an isolated polynucleotide of Claim 85.

90. (New) An isolated polynucleotide for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene consisting essentially of at least about 100 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

91. (New) The isolated polynucleotide of Claim 90, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

92. (New) The isolated polynucleotide of Claim 90, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

93. (New) A pair of isolated polynucleotides as in Claim 90.

94. (New) A kit comprising an isolated polynucleotide of Claim 90.

95. (New) An isolated polynucleotide for determining whether a subject has an increased likelihood of having the disease-associated allele 24d1 of the Hereditary Hemochromatosis gene consisting essentially of at least about 300 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphic site shown in Table 1.

96. (New) The isolated polynucleotide of Claim 95, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

97. (New) The isolated polynucleotide of Claim 95, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

98. (New) A pair of isolated polynucleotides as in Claim 95.

99. (New) A kit comprising an isolated polynucleotide of Claim 95.